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CASE REPORT

Malignant peripheral nerve sheath tumor arising from solitary neurofibroma

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ABSTRACT

Malignant peripheral nerve sheath tumors (MPNSTs) are rare sarcomas that are strongly associated with neurofibromatosis type I (NF-1). We describe a 71-year-old woman with no stigmata of neurofibromatosis, who presented with recurrent subcutaneous tumor on her left upper back. She received two excisional biopsies on the back of her trunk at our hospital and both pathology reports revealed neurofibromas. Three years after the last skin biopsy, a rapidly growing subcutaneous tumor emerged at the same site. This tumor was totally resected and the histopathology showed an ill-defined tumor in the dermis and subcutaneous tissue. The tumor was composed of spindle cells in a myxoid stroma with a transition from the area of typical neurofibroma to the hypercellular area. The hypercellular area consisted of atypical, hyperchromatic spindled cells with frequent mitotic figures. She was therefore diagnosed with MPNST.

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Introduction

Malignant peripheral nerve sheath tumors (MPNSTs; also known as "malignant schwannoma", "neurofibrosarcoma", and "neurosarcoma") are rare neoplasms of ectomesenchymal origin,[1] with an incidence of 0.001% in the general population.[2] Approximately 50% of cases are associated with neurofibromatosis type I (NF-1).[2] Most MPNSTs are found in deep soft tissue along the major peripheral nerve trunk. However, superficial forms of this tumor have been identified.[3–6] Superficial MPNST is defined as a lesion predominantly located in the dermis or subcutis without contact with the fascia.[4] Some authors have suggested that the association with NF-1 is less common in superficial forms of MPNST than in their deep counterparts.[4] Most NF1-associated MPNSTs appear to arise within pre-existing plexiform neurofibromas, which are deeply seated.[7] Non-NF-1 MPNSTs in association with a solitary neurofibroma and presenting as a superficial form have been identified.[5,6,8] Herein, we report a case of MPNST arising in a location of previously diagnosed recurrent neurofibroma.

Case report

A 71-year-old woman presented to our clinic with a 2.5 × 1.5 cm skin-colored tumor on her left upper back in May 2009 (Figure 1A). She had no clinical signs of NF-1, such as café-au-lait spots, axillary freckling, multiple cutaneous neurofibromas, and iris hamartomas (Lisch nodules) on physical examination. A family history of NF-1 or past history of radiation exposure were absent. An excisional biopsy showed some mucinous material admixed with faintly eosinophilic collagen extending in various directions, interlaced with spindle cells with elongated wavy nuclei in the dermis (Figure 1B and C). The spindle cells were positive for S-100 and neurofibroma was diagnosed (Figure 1D). There was recurrence of the skin tumor at the same site 9 months later (Figure 2A). Another excisional biopsy was done and showed a myxoid tumor embedded in thick collagen bundles in the mid to deep dermis. The tumor consisted of spindle cells with elongated wavy nuclei arranged in a whorled pattern and faintly eosinophilic collagen in myxoid stroma (Figure 2B and C). The spindle cells were positive for S-100 (Figure 2D). Recurrent neurofibroma was diagnosed. Three years later, a rapidly growing skin tumor emerged at the same site (Figure 3A). The patient received total

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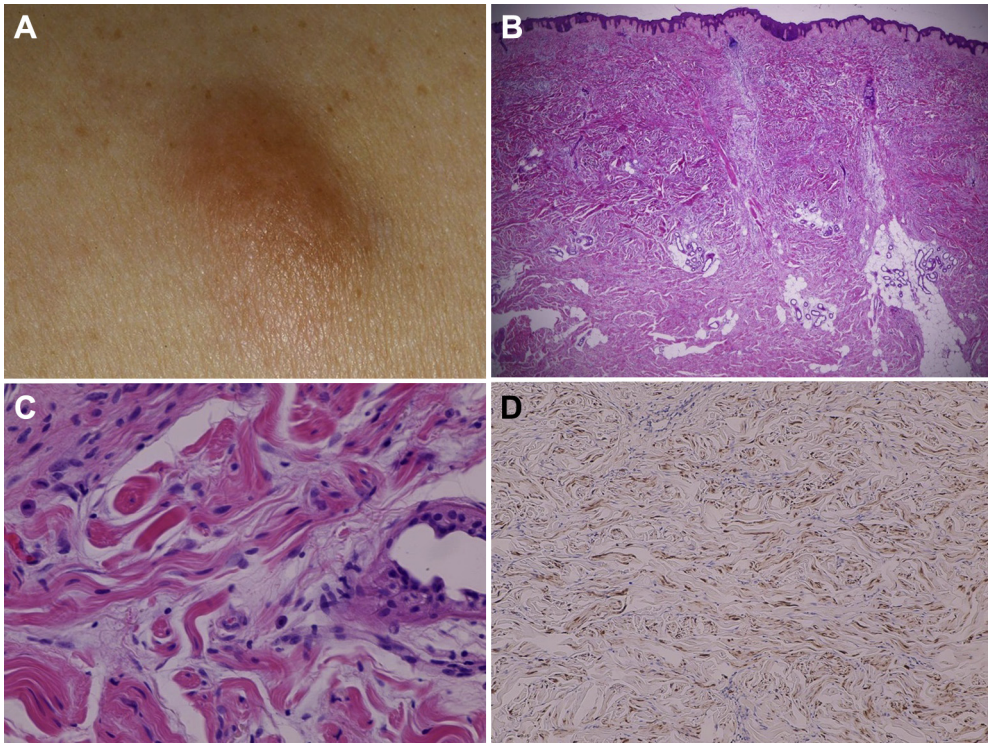

Figure 1 (A) A 2.5 cm × 1.5 cm skin-colored tumor on the left upper back. (B,C) Skin biopsy showed some mucinous material admixed with faintly eosinophilic collagen extending in various directions, interlaced with spindle cells with elongated wavy nuclei in the dermis [hematoxylin and eosin; original magnification: (B) 20×, (C) 400×]. (D) The tumor cells showed positive staining for S-100 [immunohistochemical staining; original magnification: (D) 100×].

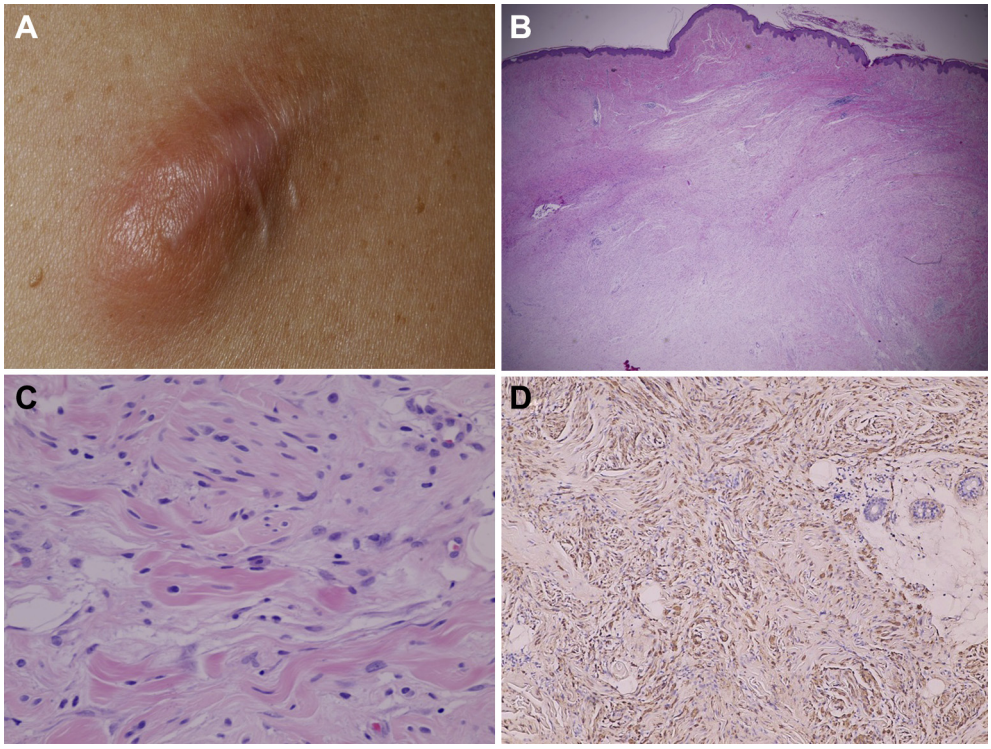

Figure 2 (A) Recurrence of skin tumor at previous biopsy site, measuring about 3.0 cm × 2.5 cm. (B,C) Skin biopsy showed spindle cells with elongated wavy nuclei arranged in a whorled pattern admixed with faintly eosinophilic collagen in a myxoid stroma [hematoxylin and eosin; original magnification: (B) 20×, (C) 400×]. (D) The tumor cells showed positive staining for S-100 [immunohistochemical staining; original magnification: (D) 100×].

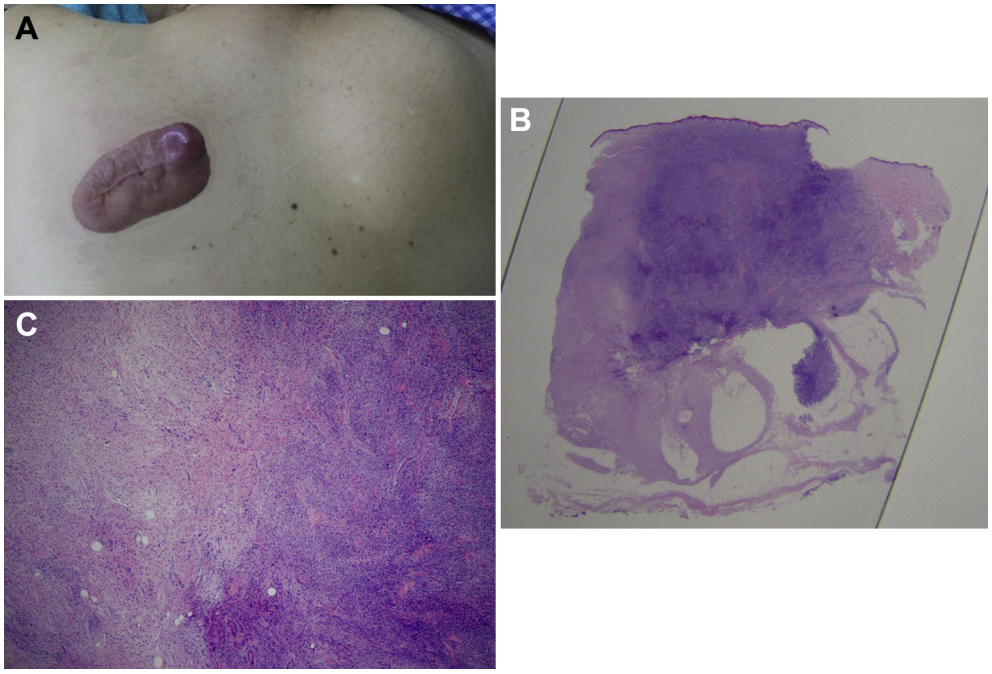

Figure 3 (A) A 5 cm × 8 cm skin tumor arising from a previous biopsy site. (B) Diffuse infiltration of tumor cells in the upper dermis to subcutaneous tissue with focal myxoid change. (C) A transition from a densely cellular area at the lower right to a typical neurofibroma at the upper left [hematoxylin and eosin; original magnification: (B) 4×, (C) 40×].

excision of the skin tumor. The pathologic report showed an ill-defined tumor in the dermis and subcutaneous tissue, measuring 5 cm × 3.8 cm × 3.5 cm (Figure 3B). Microscopically, the tumor was composed of spindle cells in a focally myxoid stroma with an obvious transition from the area of typical neurofibroma to the hypercellular area (Figures 3C and 4A). The hypercellular area consisted of atypical, hyperchromatic spindled cells with frequent mitotic figures (Figure 4B). Immunohistochemical staining revealed that the tumor cells were positive for S-100 (Figure 4C and D). Based on these findings, we made a diagnosis of superficial

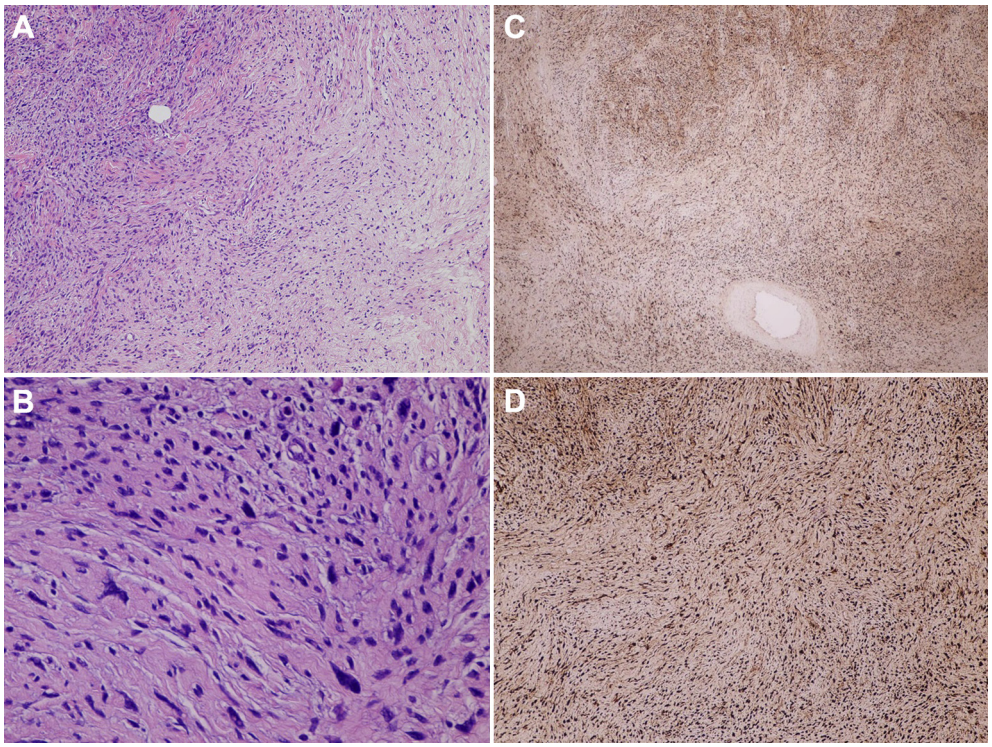

Figure 4 (A) There was an obvious transition from an area of typical neurofibroma at the lower right to the hypercellular area at the upper left. (B) The hypercellular areas of the tumor consisted of atypical, hyperchromatic spindle cells with frequent mitotic figures [hematoxylin and eosin; original magnification: (A) 100×, (B) 400×]. (C,D) The tumor cells showed positive staining for S-100 [immunohistochemical staining; original magnification: (C) 40×; (D) 100×].

Table 1 Histopathological and immunohistochemical features of spindle cell neoplasms.

Tumor type	Histopathology		Immunohistochemistry[a]				
	Gross findings	Microscopic findings	Cytokeratin	S-100	EMA	Desmin	SMA
MPNST[14]	Irregular contours; arising in a major nerve or preexisting neurofibroma	Fascicles of alternating cellularity; myxoid change may be prominent; perivascular whirling by tumor cell and hyaline nodules can be seen occasionally	−	+	+/−	NA	NA
Cutaneous leiomyosarcoma[15]	Ill-defined, diffuse infiltration	Interlacing bundles of tumor cells with eosinophilic cytoplasm and cigar-shaped, vesicular nuclei; nuclear palisading can be seen occasionally	−/+	−/+	NA	+/−	+
Monophasic synovial sarcoma[16]	Variable	Well-oriented, uniform spindle cells with tapering nuclei; focal herringbone pattern; focal hemangiopericytomatous vessels	+/−	+/−	+	−/+	−/+
Adult fibrosarcoma[17]	Well-circumscribed	Extensive herringbone pattern; no hemangiopericytomatous vessels	−	−	−	−	+, Focal

EMA = epithelial membrane antigen; MPNST = malignant peripheral nerve sheath tumor; NA = no available data; SMA = smooth muscle antigen.
[a] +, expected finding in >75% of cases; +/−, expected finding in 25–75% of cases; −/+, may be positive, but <25% of cases; −, never positive.

MPNST arising from solitary neurofibroma. The resected margins were close to the tumor cells (2–3 mm). No further follow-up information is available owing to the recent diagnosis.

Discussion

According to the World Health Organization (WHO) definition, MPNSTs are malignant tumors arising from a peripheral nerve or extraneural soft tissue with nerve sheath differentiation.[9] Approximately 50% of MPNSTs are associated with NF-1 with the remainder occurring sporadically. The incidence of MPNST among patients with NF-1 is approximately 10%.[2] In patients with NF-1, MPNSTs often arise within pre-existing neurofibromas, in particular deep plexiform neurofibromas.[10] Radiation exposure is another risk factor for the development of MPNST.[11] A superficial form of MPNSTs with a cutaneous or subcutaneous origin has been identified, and association with solitary neurofibromas was observed.[4–6,8,12] It has been demonstrated that loss of functional NF1 allele in a Schwann cell may be the initial step in neurofibroma pathogenesis, and subsequent progression from neurofibroma to MPNST is associated with additional molecular alterations.[13] However, several key steps in this process remain poorly understood.

The diagnosis of MPNST is sometimes difficult due to the histopathological similarities with other spindle cell sarcomas, such as monophasic synovial sarcoma, leiomyosarcoma, and fibrosarcoma.[2] A combination of gross, histopathological, and immunohistochemical studies can be helpful in making the diagnosis (Table 1).[14–17] Notably, each of these tumors has multiple different variants with atypical morphological characteristics and staining properties. For MPNSTs, neural markers of S-100, CD56, and protein gene product 9.5 (PGF 9.5) have been considered as sensitive markers. S-100, traditionally regarded as the best marker, was found to be expressed in only 50–90% of the MPNSTs.[18] The tumor that perhaps most closely resembles MPNSTs is synovial sarcoma.[19] Synovial sarcomas may involve nerves and MPNSTs may show glandular pattern. A history of NF1 and/or a co-existing neurofibroma precursor will aid in the diagnosis of MPNST.[19]

The prognosis is poor for the deep counterpart of MPNST and the reported crude 2-year and 5-year survival rates were 57% and 39%, respectively.[20] A recent literature reviewed 13 reported cases of superficial MPNST arising in sporadic neurofibroma that demonstrated six cases with local recurrence and two cases with lung metastases. Within the two distantly-metastatic cases, one died of tumor and the other had no follow-up after the metastases were found. Surgical resection is the mainstay treatment, but there is no available guideline regarding how much the margin should be resected around the tumor.[20,21]

In our case, superficial MPNST, which suggested an association with solitary neurofibroma, occurred in the location originally diagnosed as recurrent neurofibroma. Superficial MPNSTs are a rare variant of MPNSTs, and the lack of association with neurofibromatosis may result in superficial MPNST being overlooked. Superficial MPNST should be considered in the differential diagnosis of soft tissue malignancy of the skin, especially when there is a rapidly growing tumor arising from pre-existing neurofibroma.

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